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## Review

# Moving beyond standard procedures to assess spontaneous recognition memory



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## ABSTRACT

This review will consider how spontaneous tasks have been applied alongside neuroscientific techniques to test complex forms of recognition memory for objects and their environmental features, e.g. the spatial location of an object or the context in which it is presented. We discuss studies that investigate the roles of the perirhinal cortex and the hippocampus in recognition memory using standard testing paradigms, and consider how these findings contribute to the ongoing debate about whether recognition memory is a single unitary process or multiple processes that can be dissociated anatomically and functionally. Due to the wide use of spontaneous tasks, the need for improved procedures that reduce animal use is acknowledged, with multiple trial paradigms discussed as a novel way of reducing variability and animal numbers in these tasks. The importance of improving translation of animal models to humans is highlighted, with emphasis on a shift away from relying on the phenomenological experience of human subjects.

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## 1. Introduction

Recognition memory is commonly impaired in neurodegenerative or brain damaged patients (Aggleton and Shaw, 1996), so it is critical to gain full understanding of brain mechanisms and neural networks that are essential for this memory function in humans. The current review will discuss the behavioural approaches used to assess different forms of recognition memory in non-human animals, and how they can be usefully applied with neuroscientific approaches, such as lesions and immediate-early gene imaging, to inform our understanding of memory function in such animals. In addition, new approaches that address the large animal use in widely used behavioural tasks will be discussed. The implications for animal reduction as well as greater reliability of these tasks are significant, and sit alongside further consideration of the 3Rs (Replacement, Refinement and Reduction), in view of how animal models can be used to inform research on human memory.

A debate which is central to our understanding of recognition memory function is whether it is a single unitary process or two distinct processes. A full discussion is beyond the scope of this review, but has been comprehensively covered elsewhere (e.g. Aggleton and Brown, 2006; Clark and Squire, 2010; Ranganath and Ritchey, 2012), so we shall begin with just a brief introductory overview to provide a basis for the behavioural work to be discussed.

## 2. Recognition memory – two distinct processes?

Recognition and episodic memory are forms of declarative memory whereby memories can be consciously recalled. Recognition memory may be defined as the process of identifying when something (e.g. an object, a person) has been encountered previously. Episodic memory, on the other hand, involves memory for a past experience in one's life.

Researchers have long been interested in the mechanisms underlying recognition memory. Eichenbaum et al. (1994) proposed that recognition is supported by two functionally distinct processes mediated by structures in the medial temporal lobe; the hippocampal formation, supporting recollected associations and relationships amongst stimuli, and the parahippocampal region, supporting recognition of individual items. This functional dissociation of recognition memory was further extended by Brown and Aggleton (2001) when they proposed that the hippocampus is part of an extended circuit specifically necessary for episodic recollection (associated with a feeling of 'remembering'; Tulving, 1985), while the perirhinal cortex is part of a circuit involved in familiarity and recency judgements about an encountered stimulus (associated with a feeling of 'knowing'; Tulving, 1985). Dual-process models, such as those proposed by Eichenbaum et al. (1994) and Brown and Aggleton (2001), are based on recognition processes being functionally distinct, though there is still some debate as to which regions in the medial temporal lobe are necessary to support these processes (Eichenbaum et al., 2007). According to these models, the hippocampus, fornix (subcortical fibre pathway connecting to the hippocampus) and anterior thalamus form a neural circuit that is critically involved in the process of recollection but not familiarity. On the other hand, the perirhinal and parahippocampal cortices and the medial dorsal nucleus of the thalamus are necessary for familiarity (Aggleton et al., 2005; Bowles et al., 2007; Brown and Aggleton, 2001; Eacott and Heywood, 1995; Eichenbaum et al., 2007; Fortin et al., 2004; Langston and Wood, 2010; Ranganath et al., 2004; Sauvage et al., 2008; Yonelinas et al., 2002). However, other researchers argue that recognition memory is a single process dependent on both the hippocampus and adjacent cortex (Donaldson, 1996; Haist and Shimamura, 1992; Squire et al., 2004, 2007). Such models state recognition memory is a process

based on familiarity, where 'knowing' reflects weaker memory and 'remembering' is associated with strong memory.

Studies involving human amnesic patients with hippocampal damage have provided useful insight into this debate, with some reporting selective recollection impairment with spared familiarity processing (Aggleton et al., 2005; Bastin et al., 2004; Gardiner et al., 2006; Holdstock et al., 2002; Turriziani et al., 2008; Yonelinas et al., 2002), offering support to the dual-process model, whilst others have found deficits in both recollection and familiarity (Cipolotti et al., 2006; Jenson et al., 2010; Manns et al., 2003). To some extent, the inconsistent findings can be attributed to differences in testing measures and/or the specific medial temporal lobe damage varying between patients. If recognition memory is to be convincingly accepted as being supported by dual-processes, then it is necessary to localise the structures within the medial temporal lobe that mediate these processes, and specifically whether the roles of the perirhinal cortex and the hippocampus can be regarded as separate in their support of familiarity and recollection (Aggleton and Brown, 2006; Eichenbaum et al., 2007; Guderian et al., 2011; Montaldi and Mayes, 2010; Montaldi et al., 2006; Murray et al., 2007; Norman, 2010; Squire et al., 2007; Squire and Wixted, 2011; Vann et al., 2009; Vann and Albasser, 2011).

The human patient literature goes some way in determining the structures underlying recognition memory, however, a substantial amount of research has, and continues to be, focused on developing animal models of memory which can provide an insight into the functional neuroanatomy. The importance of such research is evident as animal studies not only allow for impairments after specific and localised lesions to be measured, but they also allow researchers to look at precise genetic and molecular factors involved in memory processes and the effect of pharmacological interventions (Dere et al., 2006), with the aim of developing appropriate treatment for memory impairments in neurodegenerative diseases, and neurorehabilitation for deficits in brain injured individuals.

## 3. Early studies on recognition memory in animals

Subjects with damage to the medial temporal lobe have been reported to experience profound memory deficits (Scoville and Milner, 1957). Early studies on recognition memory in non-human primates sought to reproduce this damage to gain an understanding of the anatomical basis for such deficits. However, the nature of a suitable task to reveal deficits which are analogous to those of patients such as H.M. was not always clear. Gaffan (1974) developed the 'delayed matching to sample' (DMS) task as a one-trial test of visual recognition memory in monkeys. The task consisted of presenting the animal with a single object in the sample phase that had to be displaced for a food reward. In the test phase, the sample object was presented alongside a new object, and the monkey was trained to select/match the object from the sample phase, thus demonstrating memory for that object. The delay between the sample and test phases of the trials could be varied to increase demand on recognition memory, and it was argued that this task was analogous to the yes/no recognition memory tasks used in human memory studies and those used to identify memory impairments in amnesic individuals (Clark and Squire, 2010).

In 1978, Mishkin modified the DMS task so that the monkeys were trained to select the new object in the test phase, rather than the object that had appeared in the sample phase. Training for this 'delayed nonmatching to sample' task (DNMS) was quicker as it capitalised on the animals' natural preference for novelty (Mishkin, 1978; Mishkin and Delacour, 1975). DNMS has been widely used as a test of recognition memory in both monkeys (e.g. Eacott et al., 1994; Mishkin and Delacour, 1975) and humans

(e.g. Holdstock et al., 2000) in order to understand the neural basis of memory. DMS and DNMS tasks have demonstrated that memory is impaired following rhinal cortex lesions (Eacott et al., 1994; Meunier et al., 1993; Zola-Morgan et al., 1989), but DNMS performance following selective hippocampal damage has offered inconsistent findings with some studies reporting DNMS deficits (Alvarez-Royo et al., 1995; Beason-Held et al., 1999; Mahut et al., 1982; Zola-Morgan and Squire, 1986; Zola et al., 2000), and others reporting no impairment following hippocampal lesions that spare surrounding cortical areas (e.g. Murray and Mishkin, 1998; Nemanic et al., 2004). Though questions around the precise role of the hippocampus in DNMS continue to be asked, there is general consensus regarding the importance of the surrounding cortical areas for successful performance.

The DNMS task has been adapted for use in rats using both objects (Aggleton, 1985; Kesner et al., 1993; Mumby et al., 1990) odours (Otto and Eichenbaum, 1992a, 1992b; Ramus and Eichenbaum, 2000; Winters et al., 2000) and computer-generated scenes (using the constant-negative paradigm; Simpson et al., 1998) as stimuli in tests of recognition memory. However, there are a number of issues relating to the use of the DNMS task with rats, as a number of lengthy training sessions are required in order for them to acquire the rules of matching or non-matching. It is important to make sure animals have acquired the rules sufficiently prior to testing, so that any deficit in task performance cannot be attributed to failing to apply them (Dix and Aggleton, 1999). In addition, as animals often receive selective food reinforcement for correct responses in the DNMS task, performance may be confounded through animals acquiring strategies to obtain the food reward; strategies which are not associated with the purpose of the task (Herremans et al., 1995). Due to the issues associated with the DNMS task it was necessary to find a way of assessing recognition memory in rodents without extensive training procedures or selective food reinforcement.

#### 4. Tasks for assessing spontaneous recognition memory in rats

##### 4.1. Spontaneous object recognition

Ennaceur and Delacour (1988) developed an alternative way of investigating object recognition in rodents using their spontaneous exploratory activity as a valid measure of recognition memory function. Similarly to the DNMS task, spontaneous object recognition tasks capitalise on the animals' innate preference for novelty as a measure of recognition. Typically, animals are individually placed in an open field with two copies of an object which they can freely explore for a period of time (Fig. 1a), often for around 3 min, though some tasks end the sample phase when total object exploration has reached a pre-set time threshold (e.g. 25 s, Winters et al., 2004). Following a delay (of minutes, hours or even days), the animal is returned to the open field arena for the test phase of the trial which contains a copy of the object seen previously and a novel object. The animal's memory for the familiar object from the sample phase is exhibited through preferential exploration of the novel object. As the animal is able to explore the physical objects, behaviour can be driven not only by visual information but also by olfactory and tactile information (Clark and Squire, 2010).

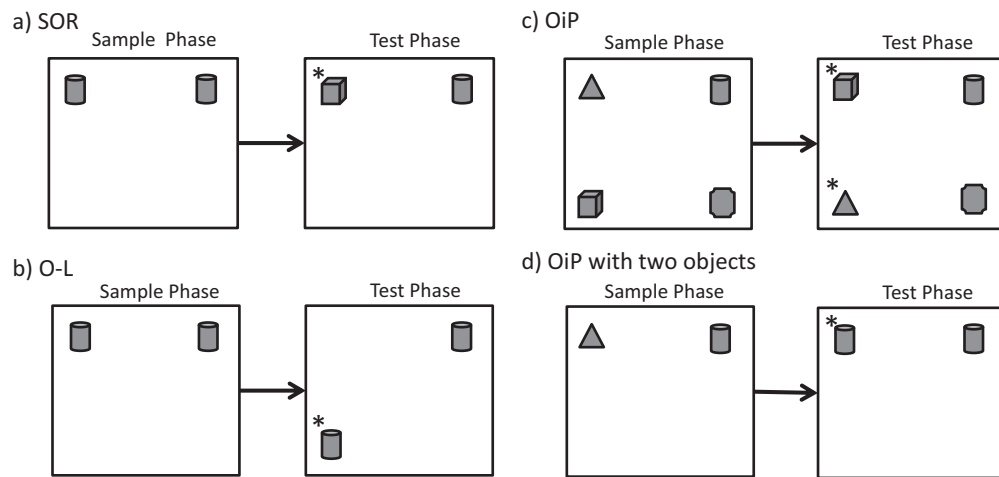
The details of spontaneous object recognition task procedures vary between laboratories and this may influence the conclusions that can be drawn. Typically, the animals are individually handled when being transferred to and from the open arena, and animals will often only perform one trial a day; a single trial consisting of a sample and a test phase. Animals may perform the task repeatedly over a few days yielding a number of trials per animal (e.g. Norman and Eacott, 2004), but some experiments have tested recognition

memory for objects with just a single trial per animal (Dere et al., 2005). Experimenters often use 3 min periods for the sample and test phases (e.g. Norman and Eacott, 2004; Barker and Warburton, 2011); this can, however, be varied with some studies opting for sample phases ranging up to 15 min (e.g. Ainge et al., 2006). Extending the length of the sample phase may serve to increase the familiarity of the exposed objects, with evidence suggesting that performance on the spontaneous object recognition task can be improved through extending the sample phase period. Albasser et al. (2009) showed that the degree of sample object exploration increased through extending the length of the sample phase, and the degree of sample object exploration was positively correlated with the degree of discrimination between the objects at test. In this study, the test phase duration was 5 min, however, the results were comparable when analysed at 2 min. These results reflect the findings by Dix and Aggleton (1999) in which they reported the most sensitive period for object discrimination with the spontaneous object recognition test phase is in the first two minutes, with object exploration significantly decreasing throughout this period.

The delay between the sample and test phase is also relevant as memory strength for the familiar object will decrease with longer delays, thus reducing discrimination performance at test. However, the absolute length over which intact rats can show successful discrimination of novel and familiar objects in this task depends crucially on the nature of the objects, in particular the similarity of the novel and familiar objects (Norman and Eacott, 2004). For example, control animals could successfully discriminate a novel object from one that had been previously explored up to 24 h ago, when the objects were standard junk objects (e.g. bottles, vases and candlesticks) which differed in many aspects (e.g. material, shape, size). However, when both novel and familiar objects were made of highly similar material (Duplo) and had been designed to share features in common with each other (e.g. arrangement of blocks into a tower), control animals could only successfully discriminate novel and familiar objects at delays of up to 15 min (Norman and Eacott, 2004).

Lesion studies using the spontaneous object recognition task have provided a useful insight into the anatomical basis for recognition memory with studies demonstrating that the perirhinal cortex is critical for successful performance on this task (Barker et al., 2007; Barker and Warburton, 2011; Bussey et al., 1999; Ennaceur and Aggleton, 1997; Ennaceur et al., 1996; Mumby and Pinel, 1994; Norman and Eacott, 2004; Winters et al., 2004). A large number of hippocampal or fornix lesion studies have reported no detrimental effect on spontaneous object recognition memory (Barker and Warburton, 2011; Ennaceur and Aggleton, 1994, 1997; Ennaceur et al., 1996, 1997; Forwood et al., 2005; Good et al., 2007; Langston and Wood, 2010; Mumby et al., 2002; Warburton and Aggleton, 1999; Winters et al., 2004), though some studies have found impairment after long delays (e.g. Clark et al., 2000, referred to as the 'visual paired comparison task'; Hammond et al., 2004). Possible reasons for the inconsistency in findings may be related to the extent of damage to the hippocampus, and/or procedural differences between studies. Ainge et al. (2006) reported that rats with either complete or partial hippocampal lesions were unimpaired on an object recognition task in which exploration of the objects was limited to 30 s during the sample phase. However, when the sample phase was defined by 15 min of free exposure to the objects, only the animals with the partial hippocampal lesions were unimpaired. Moreover, the complete lesion group showed lower levels of object exploration than the partial or control groups in the second task suggesting that not only did the extent of lesion size effect object recognition performance, but this may have also impacted on the exploration of objects at encoding.

The relative simplicity of the spontaneous object recognition task has allowed for widespread use to test recognition memory in



**Fig. 1.** Different test procedures for four spontaneous recognition tasks in the open field arena, with figures representing a single trial, consisting of a sample and a test phase. The asterisks indicate the novel object or novel configuration of the object and its spatial location. The asterisks indicate the objects in the test phase that the animals should preferentially explore. (a) The spontaneous object recognition (SOR) task. (b) The object-location (O-L) task in which one object at test occupies a novel location. (c) The object-in-place (OiP) task in which two objects swap locations at test. (d) The simplified version of the OiP task in which one object at test occupies a location previously occupied by a different object.

rodents and research suggests that the spontaneous object recognition task is more sensitive to recognition memory deficits than the DNMS task (Clark and Squire, 2010; Nemanic et al., 2004; Pascalis et al., 2004). The use of the spontaneous object recognition task across multiple disciplines can be attributed to a number of advantages. The task is very simple to administer and there is consistency of results across species (Clark and Martin, 2005). In addition, issues associated with selective food reinforcement are avoided as the object novelty is sufficient to drive exploration without being associated with a food reward.

There are, however, a number of issues related to administering tasks based on spontaneous exploration. First, as the object exploration, which serves as a measure of the animals' memory, is completely spontaneous with no prior training required, there can be considerable variance in behavioural performance between animals on individual trials. When low numbers of trials are run with each animal, the outcome of these random effects can be marked, resulting in high variability. In addition, influences other than object novelty may drive animal exploration, such as particular features of the environment around the testing arena, or initial mis-match of objects in terms of how inherently interesting they are to the animals. These factors may potentially lead to familiar, but inherently salient, stimuli being more attractive for exploration than novel, but inherently relatively unsalient, objects. Careful counterbalancing of objects, both between animals and within the test phases that each animal performs, can help to minimise potential exploration differences due to unmatched object salience. The use of D1 and D2 scores as measures of recognition goes some way in reducing potential variability in animal performance (Ennaceur and Delacour, 1988). D1 is calculated through taking the exploration of the novel object at test minus the familiar object exploration. However, D1 takes no account of differences in overall exploration levels and so results may be biased by more active animals. To account for these differences in total exploration at test, the D2 ratio is calculated: the D1 score is divided by the total exploration of both the novel and familiar object at test. The D2 ratio therefore scales the exploration to account for overall differences in total exploration. This ratio can therefore vary from  $-1$  to  $+1$  with anything above zero being indicative of novelty preference.

As spontaneous tasks rely on free exploration, stress may inhibit or change the nature of such exploration, and so may impair performance on such tasks (Yuan et al., 2009). For example, stress can result in neophobia (Ennaceur et al., 2009), and so even

the relatively small amount of stress that may be induced through handling (which may be considerable in these one trial a day tasks as animals are repeatedly taken in and out of the apparatus) may be sufficient to drive behaviour away from the novel stimulus, thereby masking true recognition abilities. Recent evidence supports this view and suggests that particular animal handling procedures can induce aversion and anxiety which can subsequently influence performance in behavioural tasks (Hurst and West, 2010). In this study, mice demonstrated greater anxiety in an elevated plus maze through reduced entry to the arms without protective walls when they were commonly handled with more anxiety-provoking methods such as being picked up by the tail.

The spontaneous object recognition task has successfully been used to study memory for objects, but the paradigm has also been adapted for testing more complex forms of recognition memory through the use of novel apparatus or task designs. Variants of the spontaneous object recognition task have successfully been used to provide evidence for functional dissociations within recognition memory, with tasks including memory for a novel combination of object and background context or object and location (e.g. Dix and Aggleton, 1999; Eacott and Norman, 2004; Ennaceur et al., 1997; Langston and Wood, 2010; Norman and Eacott, 2005). Spontaneous tasks that investigate different forms of recognition memory are a useful way of investigating the individual components that contribute to episodic memory. If we can understand the role of particular brain structures in these forms of memory then we can begin to form a picture of the potential connectivity of these structures and network interactions.

#### 4.2. Recognition memory for the spatial locations of objects

Variants of the spontaneous object recognition task have allowed memory for the object and its spatial location to be investigated. In the object-location task (Save et al., 1992), rats are exposed to two different objects in the open field during the sample phase (Fig. 1b). At test, one of the objects is moved to a novel location in the open field where an object has never been previously encountered. Intact rats preferentially explore the familiar object occupying a novel location more than the familiar object occupying the familiar location.

An alternative task, known as object-in-place (Dix and Aggleton, 1999), involves exposing rats in an open arena to four different objects during the sample phase (Fig. 1c). After a delay, the same



objects are present in the test phase but two of them have switched locations in the arena. Therefore, all of the objects in the test phase are equally familiar, and so are the locations that are occupied by objects. However, the specific combination of object and location is novel, and results in greater exploration of an object in a location that it did not previously occupy. Later variants of this task (e.g. Ameen-Ali et al., 2012; Davis et al., 2013b; Eacott and Norman, 2004) have used just two objects in the initial exposure phase, while at test there are two copies of one of these objects both occupying the same locations as the objects in the sample phase (Fig. 1d). Exploration is driven towards the object in the location it did not previously occupy (i.e. novel object-location conjunction). This variant of object-in-place therefore allows the study of memory for object-place conjunctions within a slightly simpler paradigm than that used by Dix and Aggleton (1999). This variant also allows more direct comparison with performance on the spontaneous object recognition task as there are no differences in the number of objects present, for example, and so there are no differential task-unrelated loads on memory.

The object-location task has been shown to be hippocampal dependent, as rats with dorsal hippocampal lesions (Save et al., 1992) or fornix lesions (Ennaceur et al., 1997) cannot successfully perform the task. Rats with perirhinal cortex lesions, on the other hand, show normal object-location recognition memory (Barker and Warburton, 2011). There is some evidence to suggest perirhinal involvement on the object-in-place task when the task consists of four objects and a delay of 5 or 6 min between the sample and test phases (Barker et al., 2007; Bussey et al., 2000). However, Eacott and Norman (2004) have reported successful performance on this task when two objects are used, with delays of 5 min. It is possible that the extent of lesion damage may account for the successful performance on the object-in-place task, as the studies by Barker et al. (2007) and Bussey et al. (2000) reported bilateral perirhinal lesions that were almost complete, whereas Eacott and Norman (2004) reported sparing of the caudal part of the perirhinal cortex. It is also possible, however, that a reduced memory load on the perirhinal system in the simplified task used by Eacott and Norman (2004) could also provide some explanation for the differing reports.

There are conflicting findings regarding the role of the hippocampus in the object-in-place recognition task with some studies finding impairment after hippocampal or fornix lesions (Bussey et al., 2000; Mumby et al., 2002) but others finding no impairment (Eacott and Norman, 2004; Langston and Wood, 2010). Procedural differences which result in different strategies being adopted could account for these conflicting findings; for example, Langston and Wood (2010) have suggested that the procedure adopted in some versions of the object-in-place recognition memory task allow non-hippocampally dependent (Eichenbaum et al., 1990) egocentric strategies to be employed for successful task performance while others allow only allocentric strategies. For example, in a version of the task in which the entry point into the apparatus differed on each trial, rats with hippocampal lesions were impaired compared to successful performance in the standard version of the task, in which the entry point always remained the same (Langston and Wood, 2010). Only when allocentric strategies are required, therefore, is the task dependent on the hippocampus, which may account for the differing reports on the role of the hippocampus in object-in-place recognition memory.

Overall, these findings suggest that the hippocampus may provide necessary spatial information for successful performance of object-location and object-in-place recognition memory within an allocentric framework. The perirhinal cortex is not necessary for successful performance on the object-location task, as there is no geometric change to the objects (Barker and Warburton, 2011; Mumby et al., 2002). The task, therefore, can be solved solely through the spatial information of the object's location provided

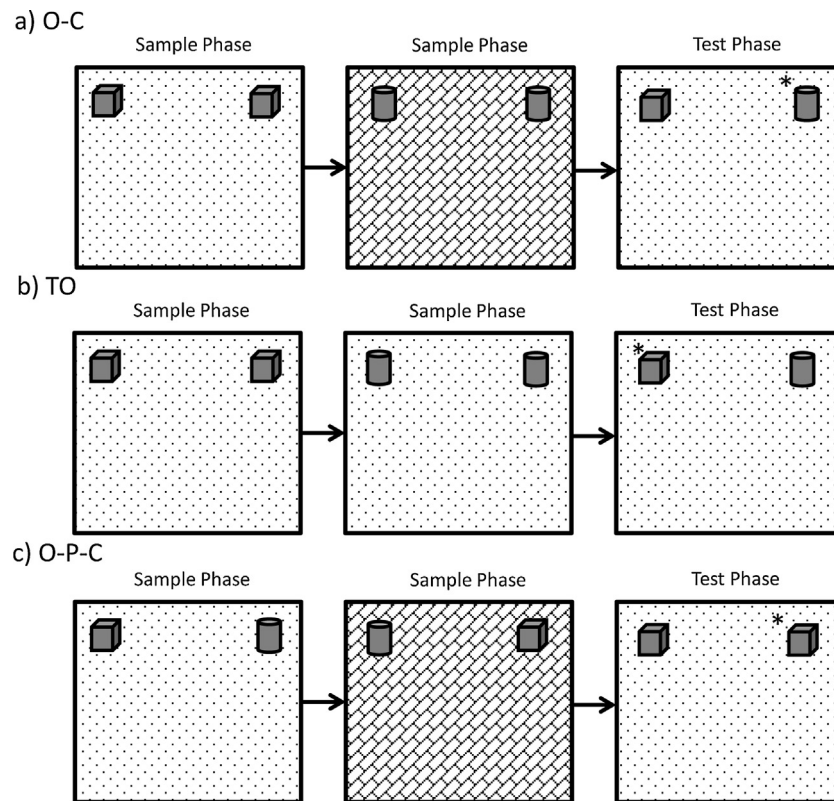
by the hippocampus (Brown et al., 2012; Dix and Aggleton, 1999). Object-in-place recognition memory has offered conflicting findings with regard to the role of the perirhinal cortex, perhaps an indication of task sensitivity to factors such as lesion size and the effect of stimuli quantity on memory load.

Work on recognition memory for objects and their spatial locations has extended beyond the use of the open field arena to the use of the radial arm maze and the Y-maze. Some researchers have argued that assessing spontaneous object recognition in the open field can be problematic, as external spatial or contextual factors from the environment external to the arena may contribute to the animal's spontaneous behaviour (Forwood et al., 2005). The Y-maze minimises these confounding factors as it has high walls and narrow arms for placing the objects to minimise the extent to which animals are influenced by external cues. The object recognition testing paradigm used with the Y-maze is similar to that used with the open field, in that spontaneous behaviour is assessed and one trial a day is performed per animal. In contrast, the 8-arm radial arm maze is designed to assess spatial working memory, whereby rats forage from baited arms of the maze and the number of errors (visits to non-baited arms or revisits to arms where food was already retrieved) is recorded. Winters et al. (2004) reported that hippocampal lesioned rats were impaired on a spatial radial arm maze task but showed normal performance on an object recognition task in the Y-maze. Rats with lesions to the perirhinal and postrhinal cortices were impaired on the object recognition task but not on the spatial radial maze task. These findings further support the role of the hippocampus for aspects of recognition that involve memory of spatial information, and the perirhinal cortex for object identification. However, in this study, memory was tested using different apparatus, with object recognition tested in the Y-maze rather than the open field to reduce any potential influence of spatial or contextual cues that might influence task performance (e.g. Aggleton and Brown, 1999; Bussey and Aggleton, 2002). However, it is also advantageous to compare both spatial and non-spatial recognition memory tasks using the same paradigm, as noted by Dix and Aggleton (1999), who argue that performance differences can be attributed to different testing procedures. Spatial memory tests continue to be widely used, but when making direct comparisons to non-spatial recognition memory tasks, the spontaneous tasks within an open field arena remain useful due to their simple design, and the potential to develop multiple testing paradigms for various forms of recognition memory in a single apparatus.

#### 4.3. Recognition memory for objects in contexts

Spontaneous tasks within the open field have also been useful for assessing the role of context in recognition memory. Contextual cues are necessary for episodic memory, so it is therefore important to first understand the relationship between context and object recognition memory. Dix and Aggleton (1999) investigated memory for objects encountered in particular contexts. In this task, rats were exposed to two copies of an object in an open field during the first sample phase (Fig. 2a). In the second sample phase, the rats were exposed to two copies of a different object in a different open field (i.e. different context). During the test phase the rats were placed in one of the open fields with copies of both of the previously encountered objects. The rats preferentially explored the novel configuration of object and context (i.e. the object at test was in a context which differed from its context at sample).

The neural basis of this object-in-context memory was investigated by Norman and Eacott (2005). Severe deficits in task performance were found following postrhinal lesions, even at very short delays of 2 min. In contrast, perirhinal lesioned animals were able to perform the task successfully at these delays, although were impaired at longer delays. Animals with fornix lesions were



**Fig. 2.** Different test procedures for three spontaneous recognition tasks in the open field arena, with figures representing a single trial consisting of sample and test phases. The asterisks indicate the novel configuration at test of the object and an aspect of the environment, such as background context, temporal order of the presented objects, or spatial location and context. The asterisks indicate the objects in the test phase that animals should preferentially explore. (a) Object-in-context (O-C) recognition task consisting of different contexts across the two sample phases. (b) Test procedure for the temporal order (TO) recognition memory task illustrating a single trial consisting of two sample phases and a test phase. (c) Test procedure for the episodic-like object-place-context (O-P-C/what-where-which occasion) recognition task.

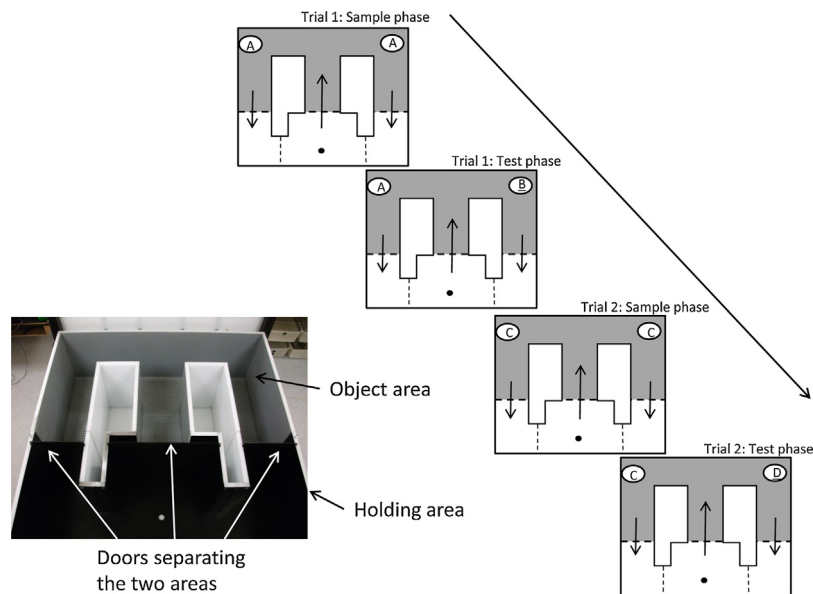
also able to perform the task at above chance levels although they were mildly impaired in comparison to sham control animals. These findings strongly implicate postrhinal cortex involvement in recognition memory of the configuration of objects and contexts. Together with those using the spontaneous object recognition task, these findings suggest there is a double dissociation between the perirhinal and postrhinal cortices. Animals with perirhinal cortex lesions are impaired on object identification (spontaneous object recognition task; Norman and Eacott, 2004) but not on recognition for the object and context configuration at short delays (object-in-context task; Norman and Eacott, 2005). Animals with postrhinal cortex lesions, on the other hand, are impaired on object-in-context but not spontaneous object recognition tasks (Norman and Eacott, 2005).

The findings by Norman and Eacott (2005) also suggest a lack of critical hippocampal involvement in the object-in-context task, as fornix lesioned animals could perform the task successfully at short delays. Langston and Wood (2010) reported similar findings with hippocampal lesioned animals, but noted that this contrasted with reports by Mumby et al. (2002) who found that animals with lesions to the hippocampus were impaired at object-in-context recognition memory. Langston and Wood (2010) offered an account for the differing reports and suggested that hippocampal involvement may be determined by how the context is defined in the task e.g. through local features such as the floor and walls of the open field, or through different testing rooms that consist of multiple features that define the environment. The hippocampus may be involved in the recognition of object and context configurations when the task involves different testing rooms to define the context, but it may not be required when the task involves discrimination between

object and context configurations in the immediate environment (Langston and Wood, 2010). Indeed, a recent study by Albasser et al. (2013) demonstrated that hippocampal lesioned rats were able to successfully perform in a biconditional learning task when the correct digging choice was determined by proximal context cues. However, deficits were observed when the correct digging choice was determined by distal room cues (Albasser et al., 2013).

#### 4.4. Temporal order/recency memory

Descriptors of episodic memory often include a temporal component (see Section 6 of this review) so it is therefore important to understand how temporal order (or recency) recognition memory is different to other forms of recognition memory before we can conceive of how this process may contribute to episodic memory. In rodents, temporal order recognition memory is often tested in the open field with animals being shown two copies of an object in the first sample phase, which they can freely explore, and two copies of a different object in the second sample phase (Fig. 2b). In the test phase, the animals are shown copies of both objects, with the expectation that the animals will spend more time exploring the object presented in the first sample phase, as it was seen longest ago and therefore is less familiar than the object seen in the second sample phase. Temporal order recognition memory has been reported as being impaired following hippocampal lesions (e.g. Barker and Warburton, 2011) and the task is also dependent on the perirhinal and medial prefrontal cortices (Barker et al., 2007; Barker and Warburton, 2011; Hannesson et al., 2004; Mitchell and Laiacina, 1998).



**Fig. 3.** Photograph of the continual trials apparatus, from above, with an example of the task procedure for spontaneous object recognition. The animal begins in the holding area (black area on the photograph, white area on the image) and enters the object area (grey area) at the start of the sample phase. The image illustrates the position of the objects. After a period of 2 min, the outer arm doors of the apparatus are opened to allow the animal to return to the holding area. Once the objects have been changed for the test phase of the trial, the animal returns to the object area, again via the central arm door. This procedure continues for each trial. The testing session ceases after the animal has completed a predetermined number of trials, or if the animal fails to shuttle to the next area once the doors have been opened for a period of 3 min. The direction of the rats' movement through the apparatus is indicated by the arrows. The letters represent object presentation from sample to test phase for two trials with novel objects underlined.

Adapted from Ameen-Ali et al. (2012).

## 5. Multiple trial paradigms for assessing spontaneous object recognition

The spontaneous object recognition task and its variants are useful ways of assessing rodent memory through the animal's spontaneous behaviour. Measuring spontaneous behaviour in the open field with the one trial a day procedure can, however, be time consuming and, as discussed above, there is significant variation in performance between animals. Studies, therefore, often require large animal numbers in order to obtain meaningful results.

One way of addressing some of the issues associated with spontaneous tasks in the open field is through a multiple trial testing paradigm. A new behavioural protocol was developed by Albasser et al. (2010a) using the 'Bow-tie maze' which combines features of spontaneous object recognition tasks with DNMS tasks. The Bow-tie maze consists of two compartments which can contain objects. The rat is placed in one compartment of the maze with one object (A). The animal then shuttles to the opposite compartment which contains two objects – one which is familiar (A) and one is novel (B). The animal then shuttles back to the first compartment which now contains object B (now familiar) and object C (novel). This sequence yields a number of trials for each animal within a single testing session. The Bow-tie maze has the benefits of a spontaneous object recognition task through using preferential exploration of novelty as a measure of recognition, with the advantages of being able to carry out multiple trials in a single session resulting in faster accumulation of data. Increasing the number of trials run per animal and decreasing potential handling stress reduces the variability in animals' performance which is associated with standard recognition tasks. The Bow-tie maze task provides a useful improvement on the spontaneous object recognition paradigm and it has, for example, been used to investigate perirhinal-based recognition mechanisms (Albasser et al., 2011). However, developing tasks of more complex forms of recognition memory with the multiple trial method in the Bow-tie maze that, for instance, may rely on a spatial component,

would make it difficult to determine whether animals were using egocentric or allocentric strategies, as each trial would involve the animal approaching the objects from the opposite side of the maze. Multiple trial tasks that combine recognition of objects with their spatial location or the context in which they were presented (e.g. Dix and Aggleton, 1999; Eacott and Norman, 2004; Langston and Wood, 2010; Norman and Eacott, 2005) are yet to be demonstrated in the Bow-tie maze, though recent work has successfully demonstrated the use of the Bow-tie maze in assessing recency memory (Kinnavane et al., 2014; Olarte-Sanchez et al., 2014) and the standard object-in-place recognition memory task (Nelson and Vann, 2014).

In light of these issues, Ameen-Ali et al. (2012) developed an apparatus that adopts the basic concept used for the design of the Bow-tie maze through combining features of the spontaneous object recognition task with features of the DNMS task, in a way that allows for further tasks of recognition memory to be tested. Within the continual trials apparatus the paradigm allows for multiple trials per session and measures recognition through preferential exploration of novel stimuli over familiar stimuli. In contrast to the Bow-tie maze, one compartment consists of a holding area, where the animal is initially placed and where it remains before and after each trial, while the other compartment consists of the object area where the testing takes place (Fig. 3). The object area can be changed to reveal a new context whilst the animal is secure in the holding area. Overall, the apparatus is designed with four contexts, making it ideal for testing recognition memory that involves context change within the procedure whilst also being able to conduct multiple trials per session. The findings from this study revealed that measures of recognition and exploration in spontaneous object recognition, object-location, and object-in-context tasks employed with the new continual trials apparatus were comparable with previous studies which have used the one-trial a day paradigm. Importantly, the new design resulted in approximately 50% fewer animals being required to obtain statistically reliable results. As



these recognition tasks are very widely used across a number of disciplines, the potential animal reduction in memory research is significant. This multiple trial recognition memory paradigm, like the Bow-tie maze, used food reinforcement of objects in order to encourage animals to continue exploration throughout the testing session, as it is important that the animals do not lose interest in the objects as the testing session continues. Object novelty may not be sufficient on its own to drive exploration in a testing session that may consist of 16 trials or more. It is important to note, however, that objects are not differentially rewarded; all objects, including those in the sample phase, are baited by placing small individual food pellets underneath objects to be displaced (Albasser et al., 2010a) or immediately in front of objects (Ameen-Ali et al., 2012). Thus the food does not reward exploration of particular objects and is therefore not driving recognition memory performance.

The successful development of multiple trial paradigms for testing recognition memory in rats opens up the potential for immediate-early gene (IEG) imaging as an approach for investigating neuronal activity associated with recognition memory. Fos protein is a product of the immediate-early gene *c-fos* and a transcription factor associated with neuronal plasticity and learning (Herdegen and Leah, 1998; Herrera and Robertson, 1996; Seoane et al., 2012; Tischmeyer and Grimm, 1999). Specifically, fos expression in the perirhinal cortex is deemed to be a reliable marker for changes in neuronal activity associated with recognition memory. Evidence suggests that fos expression in the rat perirhinal cortex increases after viewing novel visual stimuli when compared to viewing familiar visual stimuli during the paired viewing test, in which animals are simultaneously presented with novel stimuli to one eye and familiar stimuli to the other eye (Seoane et al., 2012; Wan et al., 1999, 2004; Warburton et al., 2003, 2005; Zhu et al., 1996). Although this procedure has provided insight in to neuronal activity during recognition, it can be difficult to interpret results due to lack of behavioural evidence of recognition. Using the spontaneous recognition paradigm with *c-fos* imaging would provide the behavioural measure of recognition desired, with animals actively discriminating between novel and familiar objects. This has recently been achieved with the one-trial a day paradigm (e.g. Wilson et al., 2013), however, *c-fos* activity is most readily quantifiable after many trials. *c-fos* activity has, therefore, recently been assessed using the multiple trial Bow-tie maze (Albasser et al., 2010b). *C-fos* expression in the perirhinal cortex was lower in animals tested in the object recognition paradigm using familiar objects than in animals tested with novel objects. This provides further support of perirhinal involvement in detection of object novelty. Combining behavioural approaches, such as those used in the Bow-tie maze and in the continual trials apparatus, with IEG imaging can provide stronger evidence for not only the neural basis of recognition memory, but also the network dynamics involved through the use of structural equation modelling, which can identify the direction of effects between brain structures (Albasser et al., 2010b). Work is ongoing to explore *c-fos* activation during more complex tests of recognition involving context (Wilson et al., 2013) and temporal order (Kinnavane et al., 2014; Olarte-Sanchez et al., 2014), but more work is needed to understand processes involved in tasks of object-location and episodic-like memory.

Standard versions of the spontaneous recognition tasks have been widely used by researchers to understand the neural basis of memory. Multiple trial methods offer a way to reduce the potential variability in these tasks, and in turn reduce the number of animals required in such behavioural studies. Moreover, using multiple trial methods alongside techniques such as IEG imaging demonstrates how these testing paradigms can further our understanding of memory function in the medial temporal lobe. These techniques together could, in some instances, be an alternative to traditional lesion studies. As IEG imaging simultaneously assesses activity of

multiple brain regions rather than the function of each region in separate lesion groups, this again provides potential for further reduction in the number of animals used in this research.

## 6. Episodic-like memory tasks

An episodic memory is a representation of a specific event and involves a great deal of contextual information about a specific past event in one's life (Crystal, 2010). In addition, it has been argued that conscious recollection or re-experiencing of the event is necessary for an episodic memory to occur (Tulving, 1972). As such, episodic memory has been considered by some to be unique to humans as it is said to require the ability to subjectively sense time in order to keep track of events that have occurred in one's past, but also for planning things in the future (Dere et al., 2006).

### 6.1. Memory for what happened, where and when

Tulving (1972) defined human episodic memory as remembering what happened, where and when. However, later he added the requirement that the memory included auto-noetic awareness (Tulving, 1985). This meant that demonstrating episodic memory in animals may not be possible due to the absence of language (Tulving and Markowitsch, 1998) which is needed to provide an account of subjective experience deemed necessary for assessing auto-noetic awareness (Eacott and Easton, 2010; Tulving, 2002). As such, studies on analogous processes of episodic memory in animals are referred to as "episodic-like" memory (Clayton and Dickinson, 1998), which provides a shift away from the phenomenological criteria used when assessing human episodic memory. Episodic-like memory using the what-where-when descriptor has been investigated in both Western scrub-jays and magpies by assessing their natural food caching behaviour to investigate whether they remember what type of food they have cached, and where and when it was cached (Clayton and Dickinson, 1998, 1999a, 1999b, 1999c; Clayton et al., 2001, 2003; de Kort et al., 2005; Zinkivskay et al., 2009). Demonstrating episodic-like memory in other species that do not have natural food-storing abilities is, however, considered necessary. Babb and Crystal (2005) devised a task of what-where-when memory in rats using an 8-arm radial arm maze. Animals were trained to remember the arms of the maze in which they had previously encountered food which could be recovered at either short (30 min) or long (4 h) delays. When only four of the arms were accessible, just one arm contained the preferred chocolate pellets, however, when all arms of the maze were accessible, the four previously inaccessible arms contained the less preferred food pellets. Chocolate pellets were replenished following the long but not the short delay. Rats learned to use the length of the delay as a cue for whether the chocolate arm had been replenished (and therefore would be worth revisiting), and to avoid other arms that had been previously baited. When the chocolate pellets were paired with lithium chloride (a taste aversion treatment) there was a reduction in the number of visits to chocolate-bearing arms. In combination, the authors argue the rats in this study showed memory for what, where and when, the elements of episodic-like memory. Although this study and others (Babb and Crystal, 2006a, 2006b) present evidence for episodic-like memory in rats, it has been argued that the extensive number of training trials required as part of the testing paradigm could result in rule based learning (Cheke and Clayton, 2010; Clayton and Russell, 2009). Episodic-like memory testing paradigms such as those by Babb and Crystal (2005) therefore experience the same issues associated with the DNMS task previously mentioned, in that performance may be a result of animals applying differing rules to solve the task.

Consequently, [Kart-teke et al. \(2006\)](#) devised a testing paradigm based on the spontaneous object recognition paradigm in the open field ([Ennaceur and Delacour, 1988](#)) to explore what-where-when memory in rats. As the spontaneous exploratory behaviour of the animal is assessed through their preference for novelty, no procedural training is required. The task used by Kart-teke and colleagues involved two sample phases; for the first, the animals were placed individually in the open field with four copies of an object in particular locations which they could freely explore. The second sample phase followed a 50 min delay, and again the animals were placed in the open field with four copies of a different object in different locations to those occupied previously. During the test phase that followed, the animals were exposed to two copies of the objects from each of the two sample phases, with one object from each sample phase occupying the same location it previously occupied ('stationary old' and 'stationary recent' objects), and the other object from each sample phase occupying a different but not completely novel, location than previously occupied ('displaced old' and 'displaced new' objects). The rats showed differential exploration for the displaced objects based on whether they were old or recent, suggesting these components interacted, as the authors suggest, through an integrated episodic-like memory of what (the object), where (location of the object) and when (encountered in the first or second sample phase).

However, there is ongoing debate regarding whether such memory tasks based on what-where-when are really taxing episodic-like memory. It has been noted ([Easton and Eacott, 2008](#); [Fortin et al., 2002](#); [Jacobs et al., 2013](#); [MacDonald et al., 2014](#); [Roberts, 2002](#); [Roberts et al., 2008](#)) that such tasks may in fact be solved by reference to relative memory of 'how long ago' an event occurred by keeping track of relative time elapsed since food was cached or encountered in a particular location, rather than the absolute point in time that the event occurred ([Roberts, 2002](#)). This sense of how long ago an event took place can be made via, for example, the storing of circadian oscillators with other event information ([Crystal, 2006](#)), although the relative strength of memory traces may also play a role ([Staddon et al., 1999](#)), with strong traces being associated with more recent events ([Roberts et al., 2008](#)). If memory trace is being used to define how long ago objects were encountered in the study by [Kart-teke et al. \(2006\)](#), it is possible that degraded memory strength trace for the least recent objects may account for why they would be preferentially explored during the test phase ([Easton and Eacott, 2008](#)). However, [Fortin et al. \(2002\)](#) have argued that strength of memory trace might not provide a sufficient account for why a least recently seen stimulus may be explored more or selected in a choice test. In their study, rats with hippocampal lesions were impaired on a sequential order task in which they had to select odours presented earlier in a sequence, but they were able to successfully perform discriminations between novel and familiar odours. These findings suggest that the hippocampal lesioned rats still had access to information on trace strength differences, but this was not sufficient for successful performance on the sequential order task. For the control rats, who successfully performed on both tasks, this suggests that in order to make judgements around the sequential order of the presented odours, the relative strength of memory for these items was not required. It is, however, worth noting that although the study by [Fortin et al. \(2002\)](#) demonstrates that memory trace strength may not have been required for the control animals' successful performance, it cannot be inferred that in an episodic-like what-where-when task, animals do not use trace memory strength when it is available.

Nonetheless, the definition of episodic memory includes that the memory should be of an absolute point in time that an event occurred, rather than a relative point (see [Easton and Eacott, 2008](#)). If episodic-like memory in animals is more accurately defined by how long ago an event took place, then there are fundamental

differences between human and animal experiences of these types of memories.

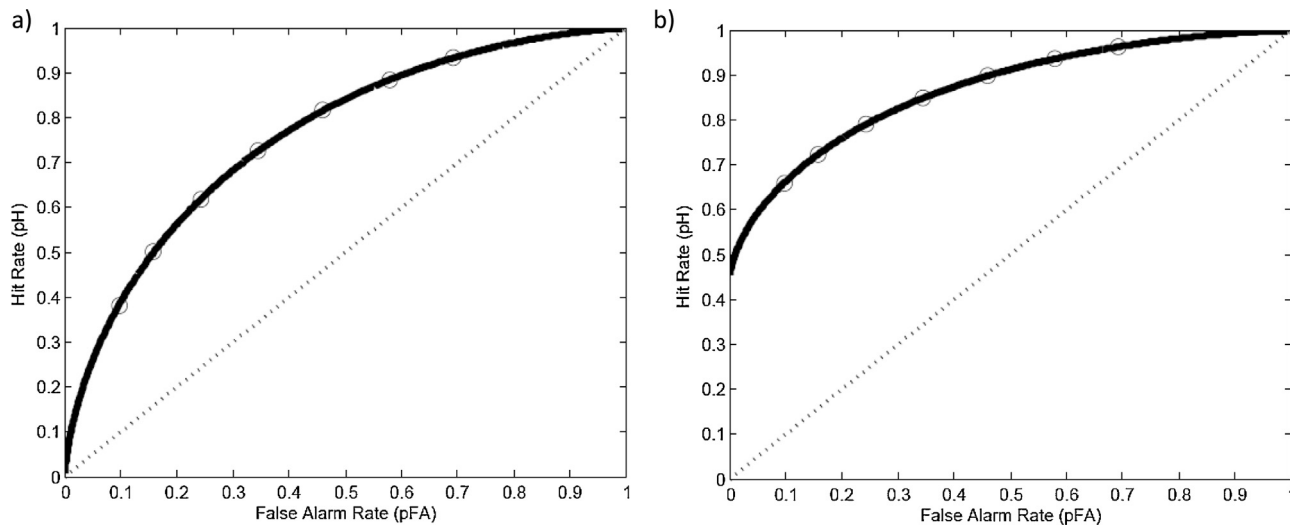
## 6.2. What happened, where and on which occasion

One way of defining a point in time is by reference to its absolute temporal reference (when). However, it has been argued that this definition is too restrictive and should be broadened to include any contextual cue that defines the point in time (or occasion) at which the specific event occurred ([Eacott and Gaffan, 2005](#); [Eacott and Norman, 2004](#)). Multiple contextual cues are often used for remembering the occasion when past events occurred, and these cues are not restricted to the specific time when something happened. Non-temporal information may also be used to indicate the occasion in which something happened; for example we may speak of an event which occurred at your graduation ceremony without reference to the date. As such, Eacott and colleagues (e.g. [Eacott and Norman, 2004](#); [Easton and Eacott, 2008](#)) have proposed a different description of episodic-like memory in animals defined as 'what-where-which occasion' memory, i.e. memory for an object (what), its location (where) and the occasion or context in which it occurred (which).

This definition has been used to investigate episodic-like memory in rats ([Eacott and Norman, 2004](#)). The authors devised a task in the open field that was a variant on the spontaneous object recognition paradigm ([Ennaceur and Delacour, 1988](#)), in which rats were exposed to two objects in a particular background context during the first sample phase ([Fig. 2c](#)). In the second sample phase, the rats were exposed to copies of the same two objects in switched locations using a different background context. In the test phase of the task, the rats were exposed to two copies of one of the previously seen objects with one of the previously seen background contexts. As such, one of these objects was presented in a location not previously occupied when in that context, resulting in a novel configuration of object-place-context (what-where-which occasion). Intact animals significantly explored this novel configuration more than the familiar one even after a 1 h delay. Fornix lesioned rats were impaired on the object-place-context (what-where-which occasion) task even at delays as short as 2 min, though the same animals could perform both object-in-place and object-in-context tasks at the same delays ([Norman and Eacott, 2005](#)). This suggests that recognition of a novel configuration of features including objects, locations, and contexts is not always hippocampal dependent, despite research suggesting that rats with large bilateral hippocampus lesions are typically impaired in recognition of object and spatial location configurations ([Good et al., 2007](#); [Mumby et al., 2002](#); [Save et al., 1992](#)), and of object and background context configurations ([Mumby et al., 2002](#)). The study by [Eacott and Norman \(2004\)](#) suggests that the memory processes underlying recognition of object-place-context configurations differ from those required for object-in-place and object-in-context configurations ([Eacott and Gaffan, 2005](#); [Langston and Wood, 2010](#)). This task provides a useful measure of episodic-like memory and has been shown to provide insight into the neural correlates of recognition memory. The task does not require any training as with previous episodic-like tasks, and has been successfully used across species (e.g. [Davis et al., 2013b](#); [Kouwenberg et al., 2009](#)). However, this task remains a recognition task and, despite strong argument that successful performance on this task requires recollection rather than familiarity ([Eacott and Gaffan, 2005](#)), it remains difficult to untangle the contributions of familiarity and recall mechanisms to successful performance in the what-where-which occasion task.

## 6.3. Recollection- and familiarity-based processes

One approach to identify the relative contributions of familiarity and recall to recognition tasks has been the analysis of



**Fig. 4.** Model receiver-operating characteristic (ROC) curves with hit rate plotted against false alarm rate across different criterion levels to illustrate potential performance on a recognition task. (a) ROC curve indicates successful recognition as the curve deviates up from the minor diagonal. The curve is symmetrical which can be interpreted as being a result of familiarity-based responses only (dual-process signal detection model) or a result of weak memory (traditional signal detection model). (b) ROC curve is asymmetrical with a high y-intercept which can be interpreted as being a result of recollection-based responses (dual-process signal detection model) or a result of unequal variance between old and new item distributions – a sign of strong memory (traditional signal detection model).

receiver-operating characteristics (ROCs). ROC curves plot hit rate (HR – when a stimulus is correctly identified as being previously encountered) against false alarm rate (FA – misidentifying a novel stimulus as being previously encountered) across a range of response criteria. If a ROC curve deviates upwards from the minor diagonal, this indicates successful recognition (Fig. 4a;  $p(\text{HR}) > p(\text{FA})$ ). Traditional signal detection theory states that recognition responses are based on a single strength variable (Squire et al., 2007), with old items representing high familiarity and new items being low familiarity (all items will have some associated familiarity based on a subject's prior experience). In contrast, dual-process signal detection models (Yonelinas, 1994) state that recognition decisions are based on either recollection- or familiarity-based processes, where the shape of an ROC curve can be used to estimate separate measurements of these components. If the curve is asymmetric, with a  $p(\text{HR}) > 0$  when  $p(\text{FA}) = 0$  (the y-intercept), this can indicate the presence of a linear (all-or-nothing) recollection threshold in addition to a curvilinear familiarity component (Fig. 4b). The y-intercept provides a quantifiable measure of recollection (proportion of old items recollection), whereas the measure of familiarity is provided by the degree of curvilinearity in the ROC, equivalent to  $d'$  in standard signal detection models.

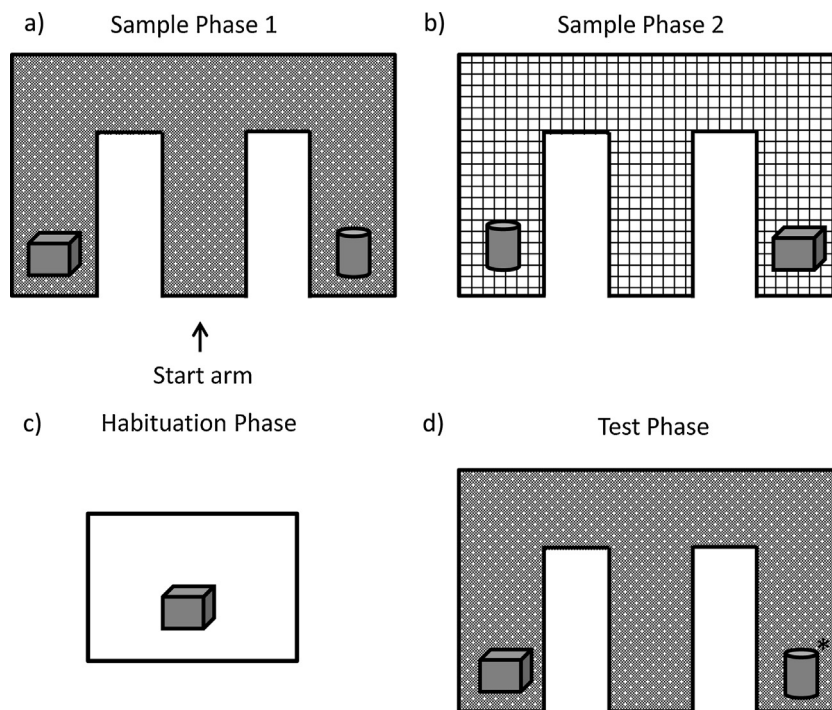
Fortin et al. (2004) used this approach in an odour recognition task in rats to assess firstly whether there are distinct recollection and familiarity processes in recognition memory, but also to investigate whether the hippocampus is selectively involved in recollection. The ROC for intact rats reflected both familiarity and recollection components, which closely matches the ROC patterns found with human recognition task performance (Yonelinas, 2001). After the animals were split into two groups—one sham group and one group receiving selective hippocampal lesions – the ROC of sham animals did not alter from the previous test. The ROC of the lesion group, however, was fully symmetrical and curvilinear reflecting familiarity-based recognition only. The findings from this study demonstrate not only that recognition memory in this task with intact rats can be based on either recollection or familiarity, but also that the hippocampus appears to be necessary for recollection. The results indicate that animal recognition memory may consist of qualitatively distinct components, as with humans (Morris and Rugg, 2004). ROC analyses can clearly be used to provide evidence of both recollection- and familiarity-based

processes, but it is also necessary to obtain behavioural evidence for this dissociation in animals.

To this end, Eacott et al. (2005) developed an episodic-like memory task using the what-where-which occasion descriptor and successfully demonstrated that the task could only be solved using recollection-based rather than familiarity-based processes. Using an E-shaped apparatus (Fig. 5), rats were individually exposed to two different objects in particular locations, in a particular background context. Rats were then exposed to copies of the previously seen objects in switched locations, and a different background context. The rats were then held in a holding cage with a copy of one of the objects, for the animal to freely explore and become habituated to it. The rats then returned to the E-maze for the test phase where they were exposed to one of the previously seen contexts, and copies of the two objects presented in the same spatial location as seen in the sample phase that featured that context. When the objects were visible to the animals from the start arm, rats preferentially explored the object that was not presented in the holding cage (i.e. non-habituated object). However, when the objects were no longer visible from the start arm during the test phase (i.e. placed around the corners of the test arms) the animals turned towards the non-habituated (relatively novel) objects at a rate significantly greater than chance. When the objects were visible, the preferential choice for the non-habituated object could be based on relative familiarity alone. The same, however, cannot be said for when the objects were not visible – to make the correct turn towards the non-habituated object the animals need to recollect the prior experience of the object locations in that particular context. The task cannot be solved solely through familiarity mechanisms, but instead rely on memory for what object was found in which spatial location on a particular occasion (represented by the context).

In a more recent study, Easton et al. (2009) investigated performance of fornix lesioned rats on the E-maze task and found that these animals did not significantly seek out the non-habituated object when the objects were not visible from the start arm, in contrast to sham lesioned animals. The fornix lesioned rats were, however, able to demonstrate normal recognition performance measured through discrimination between the habituated and non-habituated objects at test. These findings suggest that the fornix lesioned rats had impaired recollection (demonstrated through their inability to make correct turns towards objects which





**Fig. 5.** Single trial procedure example of the episodic-like memory task, based on what-where-which occasion. In the first sample phase (a), the animals can freely explore the two objects on a particular background context. In the second sample phase (b), a different context is used, and the objects have switched locations. During the habituation phase (c), the animals habituate to one of the objects for a period of 8 min. In the test phase (d), one of the previously seen contexts is used, with the objects located in the same arms they occupied in the sample phase in which that context was used. In this example, the objects are 'hidden', i.e. not visible to the animals from the start arm. Turn behaviour from the start arm is used as an indicator for recollection, as the animals should preferentially turn towards, and explore, the non-habituated object (indicated by the asterisk).

are not currently visible), but intact familiarity mechanisms which supported normal recognition performance. This might seem in contrast to the work reported by [Eacott and Norman \(2004\)](#), in which fornix lesioned rats were reported to be impaired in the open field what-where-which occasion task, whereas animals with the same lesions were not impaired in the recognition measure of the E-maze task. As noted by [Easton et al. \(2009\)](#) these different reports may be accounted for by the procedural differences between the two testing paradigms – in the test phase of the open field task, rats are exposed to two copies of the same objects, and their preferential exploration is based upon memory for what object they have explored, the objects' spatial location and background context. The task can, therefore, only be solved using episodic-like memory. During the test phase of the E-maze task, on the other hand, rats are exposed to two different, previously explored objects, although one has been habituated. Recognition is not reliant upon episodic-like memory in this measure – only object preference is needed.

As previously discussed, the hippocampus appears to play a role in spatial recognition memory ([Bussey et al., 2000](#); [Mumby et al., 2002](#); [Save et al., 1992](#)). [Easton et al. \(2009\)](#) considered the possibility that the fornix lesion impairment observed in the E-maze task may be a result of a spatial memory deficit (i.e. a single component of what-where-when occasion memory) rather than failure of the integrated episodic-like memory. For instance, it may be possible that no deficit in episodic-like memory occurred following the fornix lesions, but the animals were not able to navigate to the correct object location; the result of a spatial deficit, which is one component that integrates with other components to form an integrated episodic-like memory ([Clayton and Dickinson, 1998](#)). However, as noted by [Easton et al. \(2009\)](#), the fornix lesioned animals demonstrated no impairment in object memory, as they displayed normal levels of object exploration and object preference. When individual components of what-where-when occasion were tested in the open field, animals with fornix lesions ([Eacott](#)

and [Norman, 2004](#)) or hippocampal lesions ([Langston and Wood, 2010](#)) were able to successfully perform tasks involving recognition of object and spatial location configurations. It could therefore be inferred that any fornix lesion deficit on the what-where-when occasion open field task ([Eacott and Norman, 2004](#)) is not the result of a failure in spatial memory. The spatial demands in the E-maze what-where-when occasion task may be higher but it would be difficult to attribute fornix lesion impairment solely to a spatial deficit, as it may be possible that recall of spatial information can account for poor performance, with recall also being dependent on the hippocampus ([Aggleton and Brown, 1999](#); [Yonelinas, 2001](#)).

## 7. Translating recognition memory research to humans

The spontaneous tasks of what-where-when and what-where-which occasion are both tests of episodic-like memory in non-human animals that do not rely on evidence of conscious recollection (autoneotic awareness). Human episodic memory, however, is specifically associated with conscious recollection of an event in one's life, and thus the correspondence between the work with non-human animals and tests of human episodic memory has been questioned. Developing well-controlled behavioural methodology with animals has been necessary due to the inability to question animals about their memory experience. To be able to adopt more well-controlled tasks to study human memory will provide opportunities in some instances, but not all, for human studies to replace animal studies to assess process.

Recent studies have examined human performance on episodic-like tasks using content-based descriptors of what-where-when or what-where-which occasion ([Easton et al., 2012](#); [Holland and Smulders, 2011](#)). Such studies are important to validate the episodic memory models developed from the animal work, and to improve the translation of well-controlled behavioural work in animals to humans.



### 7.1. Episodic-like memory tasks in humans

The episodic memory descriptor of what-where-when (recall of what happened, where and when) has been extensively used in animal memory research when designing behavioural tasks of episodic-like memory. [Holland and Smulders \(2011\)](#) investigated whether human participants use episodic memory in an episodic-like memory task similar to one previously used with animals ([Zinkivskay et al., 2009](#)). Participants were asked to hide two types of items on each of two separate occasions, and they were then tested for their memory of what was hidden, where and when. Participants were asked how they recalled the information, i.e. did they remember or did they know. Remembering is associated with recollection of an event, reflecting episodic memory, whereas knowing gives a sense of familiarity, which is not episodic ([Yonelinas, 2001](#)). Participants in this task mainly reported their recollective experience as being one of remembering, suggesting that episodic memory was used to solve the what-where-when task. However, it is unclear whether task performance was related to the participant's subjective experience of remembering.

A recent study by [Easton et al. \(2012\)](#) investigated performance of human participants on recognition memory tasks used to assess episodic-like memory in animals using both the what-where-when ([Clayton and Dickinson, 1998](#)) and what-where-which ([Eacott and Norman, 2004](#)) descriptors of episodic memory. Crucially, the study by Easton and colleagues also assessed the subjective experience associated with task performance. The task was closely modelled on those used with non-human animals, and involved viewing two sequentially presented screens that consisted of a number of symbols in different locations on a distinctive background. Locations of the symbols changed between screens. Memory for either the identity (what) or location of the symbols was tested, with location being prompted by cueing to the first or second screen (what-where-when), or to the distinctive background in which it was presented (what-where-which occasion). Participants also reported their subjective experience for each judgement as being “remember”, “know” or “guess”. The results suggested that object recognition questions (what) could be answered accurately using either recollection- or familiarity-based processes, but the episodic questions based on what-where-which occasion could only be accurately answered using recollection; episodic questions based on what-where-when could be answered correctly using either recollection or familiarity. This is contrary to reports in the animal literature whereby the what-where-when task is claimed to be dependent on episodic-like memory (e.g. [Babb and Crystal, 2005](#); [Clayton and Dickinson, 1998](#)), and therefore only recollection processes. However, as discussed above, what-where-when tasks may be vulnerable to the use of non-episodic strategies such as familiarity-based trace strength information ([Roberts et al., 2008](#)). Indeed, a similar dissociation between performance on what-where-which occasion memory and what-where-when memory has also been recently reported in transgenic mice with pathology which selectively affects episodic-like memory ([Davis et al., 2013a](#)). These results together suggest that what-where-which occasion episodic-like memory tasks for non-human animals may most closely mimic human episodic memory tasks.

### 7.2. Analysis of receiver-operating characteristics

It is still debated as to whether animals remember specific personal experiences in the same way that humans experience memories of retrospective events, or whether they are more simply able to remember the facts relating to an event (in a semantic fashion), without connecting that memory to a personal experience ([Roberts, 2002](#)). With current studies on human memory, phenomenology, such as conscious recall of an event, often takes

precedent. In animals, researchers cannot demonstrate such introspection and, therefore, cognitive process is inferred from careful control of behaviour. Although the studies by [Holland and Smulders \(2011\)](#) and [Easton et al. \(2012\)](#) are important in promoting the translation of animal work on episodic memory to humans, it is also important to move away from relying on the phenomenological experience of human participants to validate episodic-like tasks.

ROC analysis has been used to distinguish between recollection- and familiarity-based processes in recognition tasks with humans using the remember/know paradigm ([Yonelinas et al., 1998](#)). With this approach, recognition confidence responses are collected alongside the number of correct responses. A recent study from our lab used ROC analysis to distinguish between and quantify the degree of recollection and familiarity components of recognition memory in human participants, in an object recognition memory task consisting of multiple conditions that are analogous to the spontaneous recognition tasks previously used with animals. Using the content-based episodic descriptor of object-location-context (what-where-which occasion) we have been able to show that the degree of recollection is significantly higher when both an object's location and context are congruent across encoding and retrieval phases of the task, relative to when only location (object-location recognition memory) or context (object-in-context recognition memory) is congruent (Ameen-Ali et al., unpublished). This study is an example of how the behavioural work used in developing animal models can be used to inform human experiments and promote better translation of studying memory process in animals to humans, without relying on phenomenology. The advantage of a task such as ours is that it removes any introspection from the participant, which is often a key, but potentially confounding, component of episodic memory tasks.

## 8. Conclusion

Spontaneous object recognition tasks have contributed greatly to our current understanding of the neurobiological basis of recognition memory, and the value of these tasks is not doubted. Despite some ongoing debate centred on particular methodological issues ([Ennaceur, 2010](#)), these tasks are very simple to administer with no required pretraining or reinforcement required. This has allowed much recognition memory research to be carried out with animals without results being confounded by potential rule acquisition or motivational issues.

Studies clearly support the view that the perirhinal cortex is necessary for object recognition memory, and plays some role in the conjunction of objects and their location and context. The role it plays in the conjunction of these features appears to be sensitive to factors such as lesion size and the feature ambiguity of the stimuli used. The contribution of the hippocampus to object recognition memory is not so clear, but evidence seems to indicate that for familiarity-based recognition the hippocampus is not essential. There is a great deal of research supporting the view that the hippocampus plays a critical role in episodic memory ([Aggleton and Brown, 1999](#); [Eichenbaum, 2000](#); [Eichenbaum et al., 1999](#); [Mishkin et al., 1997](#); [Morris and Frey, 1997](#); [O'Keefe and Nadel, 1978](#); [Tulving and Markowitsch, 1998](#)). Research is, however, ongoing to investigate how the perirhinal cortex and hippocampus interact along with other brain structures to mediate the integration of information for other more complex forms of memory. The hippocampus may be involved in integrating object information supplied by the perirhinal cortex, and spatial and contextual information processed by the postrhinal cortex. Such integration in the hippocampus may lead to the formation of episodic memories ([Bussey and Aggleton, 2002](#); [Eacott and Gaffan, 2005](#); [Eichenbaum et al., 2007](#)).

When considering the animal research dedicated to investigating episodic-like memory, a valid argument is made for defining the content as what happened on a specific occasion rather than a particular time defined by temporal order or time elapsed. Replacing the descriptor 'when' with 'which' allows for both a point in time to be specified in the episodic memory, but also other non-temporal cues to identify that point which may be just as crucial.

Research on recognition memory continues to encompass work with humans and various animal species, but most notably non-human primates and rodents. Recognition memory tasks continue to develop in terms of how animal behaviour is assessed, but also in the neurobiological techniques that can be applied alongside them. The development of new testing paradigms with the multiple trial approach maintains the advantages of being able to assess an animal's spontaneous behaviour, but reduces the variability in behavioural performance that this is often associated with. The use of such paradigms will allow key questions to be answered about recognition memory function when applied with the lesion approach, IEG imaging, or electrophysiology techniques, and research is beginning to look at different forms of memory to see how the multiple trial paradigm can be utilised. In addition, widespread use of the multiple trial paradigm can have significant implications for the 3Rs (Replacement, Refinement and Reduction), which is important for all animal research, as the reduction in animal numbers required using this paradigm has been demonstrated (Ameen-Ali et al., 2012). The use of spontaneous tasks continues to be essential for use in basic and pre-clinical research into the neural basis of memory, and animal studies remain an important contribution for informing recognition memory studies with humans.

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